BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/111,911	07/08/98	WOLD	W 16153-5587

HM12/1206

DONALD R HOLLAND
HOWELL AND HAFERKAMP LC
7733 FORSYTH
SUITE 1400
ST LOUIS MO 63105

EXAMINER	
LEE, G	
ART UNIT	**PAPER NUMBER**
1632	4

DATE MAILED: 12/06/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/111,911	William S.M. Wold
Examiner	**Group Art Unit**
Gai (Jennifer) Mi Lee	1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-25 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☐ Claim(s) _____ is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 1-25 are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice to Comply

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosure.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3,5-12,14-19,21-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to methods of inhibiting/decreasing apoptosis of a leukocytes comprises administering a recombinant adenovirus vector containing a polynucleotide encoding the Receptor Internalization and Degradation (RID) complex in a leukocytes wherein the cell expresses RID and wherein the cell expresses Fas, TNFR-1, DR3, TRAIL-R1, or TRAIL-R2 in a transplant tissue or a patient suffering from a degenerative disease or an immunodeficiency disease of both in vitro and ex vivo methodology.

As for the in vitro embodiment, the claims are not enabled as the specification fails to supply critical guidance as to the effective amounts, effective frequencies, and stability of delivery of the complex or gene, or vectors containing the RID complex sequence and promoters regulating the expression of the RID sequence to obtain an meaningful supply of expressed RID complex to the target cell. In particular, a protocol is not described for vectors comprising RID sequence that integrate into the genome and supply sufficient RID complex function to provide inhibition of cell death. The specification does not provide any readily available assays under the meaning of In re Wands that permits the determination of the complexes of RID, such as, prolong expression, cellular stability, cellular response to RID complex and cellular response to adenovirus vector. Further, there is not guidance as to the RID complex function to be supplied by any of the various examples that incorporate the RID complex usage. Without such guidance the artisan at the time of filing would not be able to implement the claimed invention without an undue amount of experimentation and without a reasonable expectation of success. The CAFC has stated the " patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that " tossing out the mere germ of an idea does not constitute an enabling disclosure" and that " the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genetech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005).

In order to justify the citation of *Genetech inc v. Novo Nordisk A/S.* And review of the relevant art at the time of filing is necessary. Fundamentally, the art taught that gene therapy was unpredictable without some parameters being given for achieving effective treatment. In particular, articles summarizing the state of gene therapy sated that expression and delivery of the gene desired for treatment were seen as the hurdles yet to be overcome (Blau et al (1995), page 1204, col. 1-2 bridg. Sent. and page 1205, col. 1-2 bridg. Sent.). Verma et al (1997) states that gene delivery is the "Achilles heel" of gene therapy, and that the ability to deliver and expression genes efficiently to obtain sustained expression is needed for effective therapy (page 239, col. 3, parag. 1.). Science News Report states that while there have been reports of convincing gene transfer and expression, there is little evidence of a therapeutic result in patients or animal models (Science (1995) 259, page 1050, col. 2, parag. 1, lines 6-15). Further, the reports stated that " there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (Science 269, p. 1050, col. 1) and that "difficulties in getting genes transferred efficiently to target cells - and getting them expressed - remain a nagging problem for the entire field" (Science 269, p. 1054, col. 3). James Wilson, one skilled in the art, stated that "'{t}he actual vectors - how we're going to practice our trade - haven't been discovered yet" (Science 269, p. 1055, col. 2). With regards to adenovirus based therapies, Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" (p. 25, col. 1) and concludes, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after

genes are delivered" (p.30). Thus, gene therapy in general was regarded as unpredictable by the art at the time of filing, and this unpredictability laid in the realm of expression and delivery of the gene.

As for modulating apoptosis, the unpredictability for the same reasons, expression and delivery of the gene of interest for therapeutic effect, was acknowledged by the art. Deigner et al. states that several studies have shown that the CD95/APO-1/Fas pathway is frequently nonfunctional in human malignancies and systemic administration can cause toxicity e.g. to CD95/APO-1/Fas-expressing liver cells (Deigner et al (1999), page 401, col. 1, parag. 3). Deigner et al. also states that the pharmacological modulation of extrinsic and intrinsic regulators of programmed cell death (PCD) in a positive or negative direction will remain a challenge to improve the efficacy of established drugs and to provide novel means to combat i.e. neurodegenerative diseases, HIV infection and atherosclerosis (Deigner et al (1999), page 410, col. 1, parag. 3). Furthermore, Tio et al. (1998) reviews this technology, and indicated at pages 205-210 that there are limitations to mammalian cell transfection. Tio et al. states that adenovirus-mediated gene therapy has a major limitation - it can elicit a cellular immune response to viral or transgene antigens that results in destruction of the transfected cells. Another problem specifically to Fas (Fas Ligand) is systemic toxicity and severe damage to the liver and even morbidity (Tio et al (1998), page 206, col. 2, parag. 5). Thus, for apoptosis gene therapy involving RID complex, at the time of filing, the stability of expression and toxicity of Fas did not provide a reasonable expectation of success by the art.

As for the *ex vivo* embodiment, the specification fails to provide guidance for some of the same reasons as set forth above. The specification does not provide any readily available working examples under the meaning of In re Wands that permits the determination of deceasing leukocyte apoptosis via cell/tissue transplantation by withdrawing leukocytes from the patient, treating the leukocytes with an effective amount of a RID complex, and administering the treated leukocytes to the patient. Most of the working examples of the specification are based on *in vitro* experiments in cell cultures with the exception of example 9. Example 9 teaches the inhibition of apoptosis of demonstrated that the vector of the invention prevents rejection of human cancer cells transplanted into immunocompetent mice (page 30, line 23-24) but this is not seen as enabling the disclosed use for the claimed method is to inhibit apoptosis because the specification discloses the invention to be a method to inhibiting apoptosis using the Adenovirus RID protein and to applied this method to include promoting survival of tissue transplants, treating autoimmune disease, and promoting tumor destruction in cancer patients. The specification, example 9, page 30-32 only states that tumor growth is observed since inhibition of apoptosis has occurred when human A549 cancer cells were injected into immunocompromise mouse but there is no indication of controls in response to mock or non-infected tumor cells with or without the administration of an adenovirus vector encoding RID complex. Furthermore, how does the example of growth of tumors in an immunocompromise mouse correlate to graft retention on the basis of modulation of apoptosis or the correlation between decreased apoptosis in tumor cells relate to decrease apoptosis in leukocytes to an effect on transplant tissue?

Without such guidance, the artisan at the time of filing would not be able to implement the claimed invention without undue amount of experiment and without a reasonable expectation of success. Again the decision by the CAFC is relevant, and is repeated here. The CAFC has stated that " patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that " tossing out the mere germ of an idea does not constitute an enabling disclosure" and that " the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See Genetech inc v. Novo Nordisk A/S 42 USPQ2d 1001, at 1005). Thus without guidance as to the method for inhibiting apoptosis by treating the cell with an effective amount of adenovirus encoding RID complex, or guidance as to cell lines which expresses Fas, TNFR -1, DR3, TRAIL-R1, or TRAIL-R2, the in vitro embodiment of the claims would require an undue amount of experimentation on the part of the artisan without a reasonable expectation of success.

Claims 4,13,20, and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention of claims 1-25 requires 231-10. Since 231-10 is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise

be readily available to the public. If 231-10 is not so obtainable or available, the requirements of 35 U.S.C. 112, regarding "how to make," may be satisfied by a deposit of 231-10. The specification does not disclose a repeatable process to obtain the 231-10 and it is not apparent if it is readily available to the public. If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that 231-10 has been deposited under the Budapest Treaty and that the virus will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit is not made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and ,

(d) a test of the viability of the biological material at the time of deposit (see 37 CFR

1.807); and ,

(e) the deposit will be replaced if it should ever become inviable.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25 contains the term "RID" is vague and indefinite such that the metes and bounds of the claims can not be readily established.

Claim 23 is vague and indefinite in its recitation of "suitable ". What exactly is consider suitable and what is not? The specification does not teach any levels which would facilitate a suitable delivery method.

The claims are free of the prior art. At the time of filing the prior art did not teach or suggest methods of inhibiting/decreasing apoptosis of a leukocytes comprises administering a recombinant adenovirus vector containing a polynucleotide encoding the Receptor Internalization and Degradation (RID) complex in a leukocytes wherein the cell expresses RID and wherein the cell expresses Fas, TNFR-1, DR3, TRAIL-R1, or TRAIL-R2 in a transplant tissue or a patient suffering from a degenerative disease or an immunodeficiency disease of both in vitro and ex vivo methodology.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gai (Jennifer) Mi Lee, whose telephone number is 703-306-5881. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (EST). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on 703-308-2035. The FAX phone numbers for group 1600 are 703-308-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

Gai (Jennifer) Lee
Patent Examiner
Art Unit 1600

Application No.: 09/111,911

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [X] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [X] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _____

Applicant Must Provide:

- [X] An initial ~~or substitute~~ computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial ~~or substitute~~ paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [ ] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE